Systematic Review of Nimodipine

To the Editor:

I noted with interest the systematic review of nimodipine from Dr. Horn et al (Stroke. 2001;32:2433–2438). The authors are to be complimented for a thorough review of difficult literature; their summary brings clarity to a previously confusing issue. I concur with their conclusions that preclinical data suggested nimodipine NOT be pursued in clinical trials.

The authors emphasized stroke infarct volume as an outcome measure. They meta-analyzed the effect of nimodipine on infarct size (their Figure 1), in which an overall favorable effect is shown for nimodipine. The "methodological score" they used to rate the quality of the reviewed articles gave a point if the article included both behavioral and morphometric outcomes.

It seems to me that this review could be taken as further indictment of morphometry as a valuable outcome measurement: infarct volume in the rodent brain seems not to predict effects either on functional outcome or in human clinical trials. This controversy has been bubbling for a while now, and this article serves to crystallize it. The only remaining arguments in favor of morphometry as an end point are (1) it is simple and (2) the data are parametric so standard statistical analysis can be used. Arguments against morphometry include (1) the variance is so huge (if it is reported honestly) that sample sizes must be increased beyond what is typically reported and (2) it has limited relevance to functional outcome. Horn et al have buttressed this latter point, perhaps unintentionally.

As we struggle to resolve the paradox of positive animal/negative human trials, we would be well served to keep this review in mind. Unless a putative neuroprotector shows effects other than reducing rodent infarct volume, it is very unlikely to prove useful in human stroke victims. I would go further and suggest that rodent infarct volumetry is useless, but I would bow to the wise and articulate rebuttals from my colleagues in this area. Nevertheless, we must now require functional improvement in animals before proceeding to clinical trials, as the authors suggest.

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Re: Stroke Therapy Academic Industry Roundtable II (STAIR-II)

To the Editor:

The second publication from the Stroke Therapy Academic Industry Roundtable (STAIR)1 is a welcome addition to the burgeoning literature on the failure of acute stroke trials. Although most of the STAIR consensus proposals are sensible and can be enacted, one is of concern, namely the suggestion that the primary outcome of acute trials should be based on a global outcome statistic, much as that used by the National Institute of Neurological Disorders and Stroke (NINDS).2 The global outcome approach combines 2 or more clinical measures (which are chosen a priori by the trialist) and is statistically efficient, ie, it can improve the power of a trial and therefore the probability of a definitive result.3 However, the statistic has no "units" and, therefore, no obvious meaning to trialists, clinicians, patient, carers, funding bodies, or society in general, except to say that a study is positive, neutral, or negative. The purpose of trials is to improve outcome through the development of new interventions, and therefore the outcome used in a study should be meaningful to those who will use or be exposed to the new treatment. The global test fails on this issue. On a related point, it is questionable whether it is ethical to consent a patient into a trial where the primary outcome is based on a global outcome statistic. When consenting a patient into a trial, we are primarily interested in conveying the potential benefit and hazard of the experimental intervention when compared with the control treatment. With respect to benefit, we should center our explanation around the trial's primary outcome, which is possible if it is impairment, disability, or dependency, and impossible if it is the global outcome statistic because there is no way to describe its meaning and significance to the patient. Interestingly, those discussing use of a global test in NINDS PROACT II and STAT trials2,4,5 that measures of dependency (modified Rankin Scale) and disability (Barthel Index) are sensitive to absolute changes of 10% or more. Indeed, given enough patients, absolute shifts of 1% in dependency can be detected, as in the acute aspirin trials.6,7

An argument given by the STAIR II panel supporting the global outcome statistic is that several outcomes of interest are analyzed together. However, conventional analysis designs can achieve the same with important dimensions of recovery being included as secondary outcomes, including impairment, quality of life, cognitive impairment, and mood.

With this reasoning, we do not need an abstract outcome. The STAIR II panel needs to review their recommendations on the global outcome statistic and instead support the use of existing and proven clinical scales. My own vote8 goes to using a measure of dependency (modified Rankin Scale) because it is easy to assess and its meaning is easy to communicate, particularly to patients during the consent procedure; this does not of course imply that this scale is perfect or that we should stop looking for better clinical measures of outcome.

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Letters to the Editor

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Response

We appreciate Dr. Bath’s careful and thoughtful analysis of the proposals raised in the STAIR-II article. His main concern seems to be in relationship to the recommendation that a global test be used in most phase III clinical trials as the primary outcome measure. We believe, based on the results of the NINDS rt-PA trial and the experience from many unsuccessful acute stroke trials, that using a global test is a reasonable approach for assessing therapeutic response in acute stroke therapy trials.

In the case of binary outcomes (as used in the NINDS) where patients are considered a success or failure on each outcome, the global approach produces an odds ratio that gives a patient or physician an indication of how the odds of a favorable outcome on treatment compares to the odds of a favorable outcome on placebo. A favorable outcome is defined as minimal to no post-stroke disability. Odds ratios are commonly used to describe treatment benefit in clinical trials when there are single outcomes, often adjusted for covariates. This is not considered unethical. If preferred, the global test can also be formulated to provide a relative risk so that the result can be explained in terms of likelihood of a favorable outcome.1 Again, relative risks are commonly used to describe treatment benefit in clinical trials with single outcomes.

The main reason to use a global approach is the concern that there is no one measure of success in stroke. A single outcome may measure only one dimension. For example, a patient may be functioning at a high level on the Barthel Index but have aphasia. We would not consider this a great treatment success. Similarly, a marked improvement may occur on a neurological assessment scale, such as the NIH Stroke Scale, but the patient might still have substantial disability, such as impaired gait.

We have been working with regulatory agencies to help them understand and accept the global approach, but we acknowledged in our article that we have not fully achieved that goal. Hopefully, in the near future, regulatory agencies will more readily acknowledge the difficulties of defining and identifying therapeutic effects with purported acute stroke therapies and agree that a global test incorporating several relevant outcome measures is a reasonable and acceptable primary outcome measure.

As an analogy to the use of a global test in clinical trials, the scientific community accepts analysis of variance where one tests for differences in means among groups and is satisfied to reject the null hypothesis, even if the individual pairwise tests are not statistically significant. With both ANOVA and in the global test, the individual tests are useful in helping to interpret the overall test. The scientific community also accepts nonparametric rank tests and their associated probability value as evidence of treatment benefit. If we used variables without categorization and used a global test that did not require binary outcomes, we would still be able to compare groups in terms of favorable outcome, although indeed we would quantify the difference in rank scores.2 The same would be true if the primary outcome was only an individual measure, such as the Rankin scale score. We generally would report a P value and rank score.

Therefore, for all of these reasons, plus those discussed in a previous article in Stroke,3 we believe that a global test derived from multiple appropriate individual outcome measures that assess a variety of outcome measures such as neurological status, disability, handicap and perhaps imaging determination of lesion size, is the best method to evaluate treatment effects of a lack of effect in acute stroke treatment trials. (Marc Fisher, MD, and Barbara C. Tilley, PhD, for the STAIR Group.)

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Effect of Age on Cerebral Blood Flow Velocity in Patients After Aneurysmal Subarachnoid Hemorrhage

To the Editor:

We read with interest the article by Torbey et al1 on effect of age on cerebral blood flow velocity in patients after aneurysmal subarachnoid hemorrhage, published in the September issue of Stroke. Using conventional transcranial Doppler ultrasonography, the authors report an unexpectedly large decrease in flow velocity in the middle cerebral artery (MCA) in patients older than 68 years in comparison to those younger than 68 years. The mean flow velocity in the MCA was found to be 42 cm/s in the former and 81 cm/s in the latter group. Thus, the difference was as much as 48%, whereas elsewhere, in other large groups of healthy subjects, the range of difference was only between 17% and 22%.2,3 The fact that the authors found a higher incidence of vasospasm in the younger group cannot explain the discrepancy because such significant differences in flow velocity were found at admission, i.e., before the vasospasm usually develops. The authors have addressed only superficially a fundamental question: why does subarachnoid hemorrhage affect cerebral vessels in older patients differently? The problem is even more intriguing given the fact that vasoreactivity appears not to be affected by normal aging.3,5

We suspect that the decline in flow velocity in reality does not need to be as substantial as the authors state. The conventional Doppler technique they used does not allow measurement of the angle of insonation of the vessel, which is crucial in their setup of the study. In young persons the horizontal portion of the MCA projects laterally toward the temporal acoustic window, whereas in older subjects it bows ventrally, which results in a wider angle of insonation.6 No exact data on the real magnitude of this angle in normal elderly subjects have been published to date. It is nevertheless important to add that our recent data7 suggest that the MCA escapes even more from the optimal line of insonation when pathologies such as intracranial arterial stenosis and/or mass are present. It is apparent that the incidence of the MCA...
atherosclerosis and/or stenosis must be higher in an older group of subjects, and it surely must have been in the group examined by Torbey and colleagues. We have found with color Doppler technique that the angle of insonation of the MCA was 47±11° on the side of its stenosis and 34±18° on the opposite side in 18 patients with MCA M1 stenosis. If we measured the flow velocity in these patients with no angle correction, the decline of the MCA from the optimal (ie, 0°) angle of insonation would introduce an error of 46% reduction of the blood flow velocity. This figure matches well the 48% of flow velocity reduction found by Torbey and colleagues in their elderly patients.

With these factors taken into consideration, our opinion is that no reliable conclusions on flow velocity in the MCA in old patients with cerebral pathologies can be drawn from measurements obtained with conventional transcranial Doppler ultrasonography. This problem can be much more reliably addressed with the use of transcranial color Doppler ultrasonography, which enables the sonographer to obtain angle-corrected blood flow velocities.

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Response
We appreciate the comments of Drs Krejza and Mariak and their interest in our article on the effect of age on cerebral blood flow velocity (CBFV) measured by transcranial Doppler ultrasound (TCD) after aneurysmal subarachnoid hemorrhage (SAH). We are in accord with Krejza and Mariak that transcranial color-coded ultrasonography (TCCS) provides angle correction and represents a reliable tool for the assessment of cerebral vasculature. Regarding their other comments on our article, we would like to offer the following response.

The first point of Krejza and Mariak concerns our finding of relatively low mean CBFV (42 cm/s) in the middle cerebral artery (MCA) in the older compared with the younger group. Despite this, most publications dealing with cerebral blood flow (CBF) measurements in healthy adults report a decline in CBF with increasing age, mainly due to a reduction of cortical CBF. In addition, CBF declines as early as 2 days after SAH compared with volunteers of the same age. The relatively high difference (48%) in the MCA CBFV between the 2 groups in our study could be explained on the basis of advanced age (older than 68 years), presence of SAH, and atherosclerosis, any of which could contribute to the lower MCA CBFV values.

It is not surprising that CBFV decreases with age. Grolimund and Seiler have described the relationship between age and MCA CBFV measured by TCD as linear using the following model: CBFV = 79.6 – 0.41age. When this formula is used in a 70-year-old hypothetical patient, the predicted MCA CBFV of 51 cm/s would not be too dissimilar to that of our older patients. Interestingly, Krejza et al., in measuring CBFV by TCCS, proposed another formula, CBFV = 93 – 0.67age, which would estimate CBFV of 46 cm/s in a 70-year-old patient, equal to our own findings.

Krejza and Mariak raise questions about clinical value of the conventional “blind” TCD technique, specifically during MCA insonation in the elderly because of the lack of a visual image and ability of angle correction. Clearly, the addition of a visual image will improve evaluation of cerebral hemodynamics, but this does not negate the usefulness of conventional TCD. Conventional TCD has proved to be sufficiently sensitive and accurate to detect intracranial stenosis (including MCA) for patients of all ages. Since we used a blind TCD technique, it is impossible to ensure the same angle of insonation. However, once an audible Doppler signal is obtained, efforts routinely are made to acquire the strongest and highest-intensity Doppler signal possible by skilled ultrasonographers using visual waveform and audible feedback from the signal itself. The depth and angle of insonation yielding the best signal are then used as a starting point for each individual on subsequent studies. The TCD probe has a smaller diameter than that of the relatively large probe used with TCCS and can be easily manipulated at a variety of angles in all planes to optimize the signal. These maneuvers may lead to the optimal angle of insonation and maximal mean CBFV in most cases.

The final issue is more sensitive. Krejza and Mariak make the strong assertion that TCD is limited for diagnosis of CBFV and favor TCCS. We would speculate otherwise at this point, especially in the elderly. It is well known that hyperostosis of the temporal bone is influenced by age, sex, and race. TCCS has a relatively high failure rate with the use of the transtemporal approach. The transtemporal window is not found in 30% of those older than 60 years with the use of TCCS. The failure rate of transtemporal insonation was 23% in the study of Martin et al., using TCCS compared with 16% on the basis of a survey of transtemporal insonation in 11006. One of the reasons for a relatively high (23% to 30%) rate of unsuccessful insonation through the temporal bone in the elderly could be the relatively large surface of the TCCS probe, which limits the degree of freedom for limited temporal window insonation compared with the small surface of the conventional TCD probe. At the present stage, relatively high TCCS failure may prove a factor limiting the use of TCCS for imaging the anterior cerebral circulation in the elderly. The use of echo-contrast agents may partly overcome such difficulties by facilitating imaging in the future.

Direct comparisons between TCD and TCCS are limited. In a work by Krejza et al., baseline MCA CBFV value measured by TCCS for the younger population is identical (81 cm/s) to our value, which was obtained with the use of conventional TCD technique. In a study comparing the 2 techniques directly in healthy volunteers, Shoning et al. observed that CBFV for the MCA was 61 ± 13 cm/s by conventional TCD and 58 ± 12 cm/s by TCCS. Barrels and Flugel and Proust et al. showed that angle-corrected systolic CBFV values were higher in all vessels compared with uncorrected systolic CBFV findings by conventional TCD; however, the standard deviation was high for both methods, and there were no statistically significant differences. Proust et al. also showed that there was no difference in mean

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CBFV between TCCS and TCD. Therefore, available data do not support a clear overall benefit of either technique. Krezja et al stress the importance of their recent data that suggest that the MCA is distorted from the optimal line of insonation in patients with stenosis or mass effect. However, their data set consisted of a relatively young population (median age, 53 years) with a wide age range of between 22 and 72 years. Furthermore, the significant angle of insonation (47° ± 11°) reported was the average for patients with stenosis (n=11) and intraparenchymal hematoma (n=6). Grouping does not allow separate analysis of elderly patients in this study. Since the presence of an intracranial mass (tumor, hematoma, hydrocephalus) could severely influence the location and consequent insonation of the MCA, their overall mean angle of insonation may be shifted to a higher value than MCA stenosis alone.

In the final analysis, we believe that the age factor should not be ignored in the attempt to establish CBFV thresholds for the diagnosis of cerebral vasospasm. Both TCD and TCCS techniques are exciting developments in neurosonology. However, we cannot yet validate the superiority of one over the other. Both methods have their intrinsic benefits and limitations that must be recognized by all users. The availability of TCCS devices is still limited because of the relatively high cost. Some disagreements between the diagnostic findings of conventional TCD and TCCS methods need further evaluation and validation by other CBF studies as well as direct comparison of the techniques in expert hands.

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Conjugate Eye Deviation With Head Version due to a Cortical Infarction of the Frontal Eye Field

To the Editor:

Conjugate eye deviation (CED) occurs in approximately 20% of patients with cerebrovascular disease. CED is usually caused by a certain degree of hemispheric lesion subside aphasia, hemiparesis, or coma, which indicates poor prognosis. The underlying mechanism of CED is thought to be a disturbance of the cortical center or subcortical pathways involved in the control of voluntary eye movements. However, the exact site of the human frontal eye field (FEF) is still controversial. In this letter...
we discuss the possible location of the FEF of human response to CED in a patient with localized cortical lesion.

An 82-year-old woman was admitted to the hospital for acute-onset visual disturbances. She reported the sudden appearance of visual disturbance that she felt as difficulty of fixation to her left side. General examination showed arterial blood pressure of 170/100 mm Hg and pulse rate of 72 beats/min. Neurological examination showed the eyes were deviated to the right, but there was difficulty in turning the eyes and head to the left side, although both eyes responded to horizontal oculocephaloplastic stimulation. In addition, the neck rotated to the right. Spontaneous ocular nystagmus was observed, however, there was no facial palsy, dysarthria, or dysphagia. The patient did not complain of any muscle weakness, and neurological examination revealed no motor signs and no abnormal reflexes. The Mini-Mental State Examination score was 21, and neuropsychological examination revealed no hemispatial agnosia. CED diminished on day 2, although persistence of left horizontal gaze palsy was noted. All symptoms disappeared 4 days after commencement of treatment.

MRI was performed on a 1.5-T Magnetom Vision system (Siemens Medical Systems) 16 hours after onset of symptoms. T2-weighted images of the brain did not detect any specific lesions in suspected areas including the brain stem, although right-sided CED was identified (Figure A–C). However, diffusion-weighted images successfully identified a localized cortical lesion in the caudal part of the right middle frontal gyrus (Figure D). Further examination of the affected lesion with fast fluid-attenuated inversion recovery on day 19 showed the lesion extended from the junction between the superior frontal sulcus and precentral sulcus (Figure F).

The clinical features and response to therapy in our patient are consistent with a transient ipsilateral CED with right-sided head version due to a localized cortical infarction in the right middle frontal gyrus. A sudden imbalance between the left and right tonic frontal inputs on the superior colliculus and/or premotor reticular formations of the brain stem is the probable mechanism of the initial eye deviation observed after an acute frontal lesion. A rapid adaptation involving both the opposite frontal lobe and the cerebellar or brain stem structures may explain the relatively brief nature of eye deviation. Tijssen et al. postulated the oculomotor centers are asymmetrically organized in the two hemispheres: diffuse on the left and focal on the right. Our case suggests that a localized lesion resulted in CED because of the involvement of the right hemisphere.

The anatomic area responsible for the symptoms has been traditionally believed to be Brodmann’s area (BA) 8. This assumption is based on experimental findings that electrical stimulation of the FEF evokes contralateral eye movements. Paus et al. evaluated the location and possible function of the human FEF by reviewing the results of cerebral blood flow (CBF) and lesion studies with positron emission tomography and MRI and challenged the commonly held view of the FEF being located in BA 8. The medial cluster of CBF-defined FEF peaks were detected at the junction of the superior frontal sulcus and precentral sulcus, and thus, the eye movement field proper lies in BA 6. Subsequent studies using functional MRI and transcranial magnetic stimulation supported these findings (Figure E). The affected lesion in our patient also corresponded to BA 6, which is the junction of the superior frontal sulcus and the precentral sulcus (Figure F).

Our patient presented with simple right CED with right-sided head version. Goodwin and Kansu reported deviation of the eyes was also occasionally accompanied by deviation of the whole head, which rotates to a greater or lesser degree around the axis of the neck such that the face is turned toward the shoulder of the nonparalyzed side. Furthermore, Godoy et al. showed head version was accompanied by eye deviation during electrical stimulation of the FEF in more than half of their subjects. This finding suggests that the FEF is likely to be located close to the areas that control head movement or is part of the same functional area. The relationship between the direction of eye deviation and head version suggests that the sternocleidomastoid muscle receives bilateral hemispheric innervation and that the maximal input originates from the ipsilateral hemisphere.

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Overall Crude Mean (±SD) SF-36 Scores for Patients at 12 Months, and Overall Summary Mean Scores for the Duration of Follow-Up, for the “Early Hospital Discharge and Home-Based Rehabilitation” (HBC) and “Conventional Care” (CC) Groups

<table>
<thead>
<tr>
<th>SF-36</th>
<th>Patients</th>
<th>Caregivers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12-Month Scores</td>
<td>Study Duration*</td>
</tr>
<tr>
<td></td>
<td>HBC (n=39)</td>
<td>CC (n=38)</td>
</tr>
<tr>
<td>Physical Component Summary Score</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>39 (11)</td>
<td>40 (10)</td>
</tr>
<tr>
<td>Mental Component Summary Score</td>
<td>53 (11)</td>
<td>55 (9)</td>
</tr>
<tr>
<td>Physical Functioning</td>
<td>39 (29)</td>
<td>44 (30)</td>
</tr>
<tr>
<td>Role Physical</td>
<td>82 (34)</td>
<td>78 (35)</td>
</tr>
<tr>
<td>Bodily Pain</td>
<td>68 (28)</td>
<td>74 (32)</td>
</tr>
<tr>
<td>General Health</td>
<td>55 (28)</td>
<td>67 (24)</td>
</tr>
<tr>
<td>Vitality</td>
<td>52 (22)</td>
<td>54 (24)</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>83 (30)</td>
<td>89 (24)</td>
</tr>
<tr>
<td>Role Emotional</td>
<td>94 (17)</td>
<td>89 (26)</td>
</tr>
<tr>
<td>Mental Health</td>
<td>78 (20)</td>
<td>82 (17)</td>
</tr>
</tbody>
</table>

*Difference (95% CI)

*Area under the curve (AUC) summary statistics measured at 3, 6, and 12 months post-randomization. Negative differences indicate lower (worse) scores for the HBC group. No data for one patient in the HBC group and for one caregiver in the CC group.

Of the 86 randomized patients with acute stroke, 2 were lost to follow-up (CC group) and 7 died during follow-up (HBC=3, CC=4), resulting in 77 subjects available for review at 12 months: 39 in the HBC group and 38 in the CC group. There were no significant differences between the groups on average age, gender, medical history, living arrangements, or activity of daily living scores at baseline6 or at 12 months. For the group, ages ranged from 28 to 88 years (mean ± SD, 71 ± 11 years, with 3 patients aged under 50), 56% were male, 42% lived alone, and 52% had caregivers.

The Table presents data for patients and caregivers on the SF-36. Cross-sectional and AUC SF-36 mean scores were similar for the 8 domains and the 2 summary scores at 12 months. However, confidence intervals (CI) were wide for all outcomes. The only significant difference between groups occurred in cross-sectional scores for the general health domain with the HBC patients scoring less than CC patients (12-point difference, 95% CI −23.9 to −0.1).

These data suggest that early hospital discharge and home-based rehabilitation result in broadly similar health outcomes to conventional in-hospital rehabilitation, discharge, and follow-up care for patients and caregivers following acute stroke. Although cross-sectional comparison of caregiver outcome at 6 months indicated poorer mental health in the intervention group, the current analyses, both cross-sectionally and taking into account full follow-up data, do not indicate any major adverse effect on caregivers. It is likely that the earlier difference in scores for mental health in caregivers, and now on the general health domain of the SF-36 in patients at 12 months, are chance findings.

A major limitation of this study is that it lacked sufficient power to detect small-to-moderate differences between the 2 groups. Although our finding of no significant differences between patients and caregivers up to 1 year after randomization is consistent with other data, previous studies have included small numbers of participants and, therefore, the conclusions should be interpreted with caution. Caregiver outcome, in particular, requires closer attention, as to date there have been few studies with the capacity to relate patient and caregiver characteristics to long-term caregiver outcome.
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Systematic Review of Nimodipine
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